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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **STEREOSPECIFIC REDUCTION OF SAPOGEN-3-ONES**

(57) Abstract: A method to stereospecifically prepare a steroidal sapogenin or a derivative thereof by reducing a 3-keto,5 β -H steroidal sapogenin with a hindered organoborane or an organo-aluminium hydride. A 3 β -hydroxy,5 β -H steroidal sapogenin or derivative thereof may be prepared by reducing the 3-keto,5 β -H steroidal sapogenin using as reducing agent a relatively highly hindered organoborane reagent or by S_N2 inversion of a 3 α -hydroxy,5 β -H steroidal sapogenin or derivative thereof. The organo-aluminium hydride may be used to prepare a 3 α ,5 β -H steroidal sapogenin or derivative thereof. The invention provides a convenient route to useful steroidal sapogenins such as sarsasapogenin, episarsasapogenin, smilagenin, epismilagenin and esters thereof, from readily available or easily preparable starting materials (e.g. diosgenone, preparable from diosgenin).

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, EMBASE, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 703 052 A (MCCARTHY PETER ANDREW ET AL) 30 December 1997 (1997-12-30) column 20, line 24-46 ---	1-19, 23, 25
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Y	US 5 939 398 A (DENINNO MICHAEL PAUL) 17 August 1999 (1999-08-17) column 22, line 47-63 ---	1-19, 23, 25
Y	US 6 150 336 A (DENINNO MICHAEL P ET AL) 21 November 2000 (2000-11-21) column 29, line 15-24 ---	1-19, 23, 25
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAJIS NORDIN H ET AL: "Epi-sarsasapogenin and epi-smilagenin: Two sapogenins isolated from the rumen content of sheep intoxicated by Brachiaria decumbens." STEROIDS, vol. 58, no. 8, 1993, pages 387-389, XP002237585 ISSN: 0039-128X page 388, column 1, paragraph 4 ---	1-19, 23-25
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Y	K. MORITA : "Studies on the Sapogenins of Dioscorea tokoro Makino. III . Synthesis of Isorhodeasapogenin and Some Reactions of Tokorogenin" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 32, no. 8, 1959, pages 796-799, XP002260964 TOKYO JP page 796, column 1, reference number (1) to Bulletin of the Chemical Society of Japan, Vol 32(8) pp 791-795, indicates that this document is a continuation of that earlier document page 797, column 2, last paragraph -page 798, column 1, paragraph 2 ---	20-22, 25
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	F. C. CHANG ET AL: "Acyl Amides as Epimerization Reagents" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 80, 1958, page 2906 XP002260966 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 2906, column 1, paragraph 4 -column 2, paragraph 3 ---	20-22,25
Y	DROGEMULLER, MICHAEL ET AL: "Steroidal pyrazines, synthetic advances and biological activity" PROCEEDINGS OF ECSOC-2: THE SECOND INTERNATIONAL ELECTRONIC CONFERENCE ON SYNTHETIC ORGANIC CHEMISTRY, SEPT. 1-30, 1998 (1999), 209-225, 'Online! XP008024423 Retrieved from the Internet: <URL:http://www.mdpi.org/ecsoc/> 'retrieved on 2003-11-11! page 9, Scheme 6, paragraph 1 - note the document on file is a computer print out with pages numbered 1-17, whereas the published proceedings the relevant page numbers are as above (209-225) ---	20-22,25
Y	GOBBINI M ET AL: "Digitalis-like compounds: synthesis and biological evaluation of 3beta-(aminoalkylthio) derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 4, 18 February 1997 (1997-02-18), pages 469-472, XP004136048 ISSN: 0960-894X page 470, scheme 1 ---	20-22,25
Y	J. C. BABCOCK ET AL: "Reductive Methylation of Steroid Ketones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 74, 1952, pages 5472-5474, XP002260967 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 5474, column 2, paragraphs 2-4 ---	20-22,25
X	WO 02 079221 A (HU YAER ;XIA ZONGQIN (CN); PHYTOTECH LTD (GB); GUNNING PHIL (GB);) 10 October 2002 (2002-10-10) cited in the application example 6 --- -/--	1,5-19, 24,25

INTERNATIONAL SEARCH REPORT

PCT/GB 03/01780

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TOCHTROP GREGORY P ET AL: "Synthesis of '3,4-(13)c(2)!-enriched bile salts as NMR probes of protein-ligand interactions." THE JOURNAL OF ORGANIC CHEMISTRY. UNITED STATES 20 SEP 2002, vol. 67, no. 19, 20 September 2002 (2002-09-20), pages 6764-6771, XP002260968 ISSN: 0022-3263 page 6768, schemes 4,5 ---	1,5-19, 24,25
Y	WEET J F ET AL: "MINERALOCORTICOID PROPERTIES OF POTENTIAL METABOLITES OF 18 HYDROXYDEOXYCORTICOSTERONE AND 18 HYDROXYPROGESTERONE" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 2, 1985, pages 233-239, XP002260969 ISSN: 0022-2623 page 234, scheme I ---	1,5-19, 24,25
Y	C. DJERASSI ET AL: "Steroidal Sapogenins. XIII. Delta-8(9)-22-Isospirosten-3.alpha.-ol" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 28, no. 2, 1952, pages 422-424, XP002260970 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 423, column 1, paragraph 1 -page 423, column 2, paragraph 3 -----	24

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-12, 15-17, 20-22, 25 (searched in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,6-19,25 (in part) 2-4,23 (in full)

Method for the stereoselective reduction of sapogen-3-one compounds to the corresponding sapogenins using a hindered organo-borane reducing agent.

2. Claims: 20-22 (in full) 25 (in part)

Method for the stereoinversion of 3.alpha.-Hydroxy-sapogenin compounds to the corresponding 3.beta.-compounds, by reaction of an activated derivative thereof with a Nucleophilic agent.

3. Claims: 1,6-19,25 (in part) 5,24 (in full)

Method for the stereoselective reduction of sapogen-3-one compounds to the corresponding sapogenins using a organo-aluminum hydride reducing agent.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-12,15-17,20-22,25 (searched in part)

The term "steroidal sapogenin" as used in claim 1 used to define the starting material and products of the process process of claim 1 of both claimed inventions 1 and 3 and in claim 20 to define the starting material and product of the process of claimed invention 2 has no well recognised meaning in this technical area (steroid chemistry). In this regard it should be noted that the fact that this term may be used in the art (in particular in the patent literature) does not necessarily mean that it has a well recognised meaning. Consequently, the use of this term to define the starting materials and products of the process of claim 1 renders this claim extremely unclear according to Article 6 PCT. This term is of such an unclear nature, that the basic chemical structural features of starting materials and products are unknown to an extent that it is not possible to know whether or not all structures of starting materials and products (and hence all processes of claim 1) would have been covered by the search.

Consequently the search on claimed inventions 1 and 3 has been limited to the process of claims 13 and 18, 19 and 23, where the products of the process (and by implication the starting materials) are sufficiently identified (by name or by means of a structural formula). The processes of claims 1-12 and 15-17 are only searched in so far as they the same in scope as claims 13, 18, 19 and 23.

Furthermore, the search on claimed invention 2, claims 20-22 and 25 in part, has been limited to the stereoinversion of 3.alpha.-hydroxy, 5.beta.-spirostan derivatives to the corresponding 3.beta.-Hydroxy derivatives, this limitation covers the subject matter of examples 9 and 10. This limitation is based on the statement made on page, lines 11-23 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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